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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/755,205	01/04/2001	Xiangzhong Yang	UCON-150	4832

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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,205	YANG ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *46-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *46-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

New claims 46-66 [2/12/2004] are pending and under examination.

Claims 1-35 were canceled by applicants [6/27/2003].

Claims 36-45 were canceled by applicants [2/12/2004].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46, 48-51, 54, 55, 58 and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Martino et al. {IDS reference; Biology of Reproduction. 1996. 54:1059-1069).

Claims are directed to a method for cryopreservation of oocytes comprising steps of suspending oocytes in an equilibration medium, rinsing the oocytes in a vitrification solution, vitrifying the oocytes by dropping microdroplets of the oocyte suspension onto a solid surface that has a temperature between -150 degree C and -180 degree C and collecting frozen microdroplets that contain vitrified oocytes. Some claims are further drawn to rinsing for 25-30 seconds. Some claims are further drawn to the use of vitrification solution that comprises intracellular cryoprotectant or ethylene glycol, sugar, macromolecule and surfactant. Some claims are further drawn to the use of ethylene glycol as cryoprotectant and serum as surfactant. Some claims are further drawn to the use of microdroplets having volume of about 1 microliter.

The reference by Martino et al. discloses a method for cryopreservation of oocytes by rapid/ultra rapid cooling or by dropping microdroplets of the oocyte suspension onto a solid

surface of metal grids that are immediately plunged into the liquid nitrogen having temperature about -150 to -180 degree C (page 1061, col.1, last par.). The microdroplets have volume of about 1 microliter. The oocytes suspension is obtained by suspending and rinsing the oocytes in solutions EG5.5 or EG4 that comprise ethylene glycol (EG) as an intracellular cryoprotectant, sucrose as a sugar and serum from the oocyte medium wherein serum is a surfactant and a source of protein macromolecules (page 1061, col. 1, par. 1). The oocyte rinsing time is about 30 seconds (page 1061, col. 2, par. 1, last line). The frozen microdroplets were collected and further thawed at 37 degree C for 1 minute and subjected to IVF (page 1061, col. 1, par. 2). The cryopreserved oocytes maintain viability and morphology (page 1063, col. 1, par. 4, lines 1-3). The cryopreserved oocytes have the same fertilization rate as oocytes without cooling (abstract). The base medium TCM 199 is used for making oocyte suspension (page 1060, par. 3).

Although the cited reference does not clearly distinguish between equilibration and vitrification solutions, the EG5.5 or EG4 solutions that are used for making or suspending and for rinsing the oocyte suspension comprise the same functional ingredients as required in the claimed method. The oocytes are subjected to cryopreservation by rapid cooling after oocyte exposure for the same time to the same functional ingredient-containing solution(s) as required for the claimed method. The final product of the cited reference maintains viability and morphology as required by the final product of the claimed invention. Thus, the method of the cited reference anticipates the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 46-51, 54-62 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martino et al. {IDS reference; Biology of Reproduction. 1996. 54:1059-1069} and Papis et al. {IDS reference; Theriogenology. 1999, page 173.).

Claims 46, 48-51, 54, 55, 58 and 64-66 as explained above. Some claims are further drawn to the use of an equilibration solution with EG as intracellular cryoprotectant for about 12-15 minutes at near physiological temperature of about 39 degree C. Some claims are further drawn to the use of oocytes that have cumulus cells removed, to thawing time of about 3 minutes at temperature of about 39 degree C, to the use of non-human mammalian oocytes, to further fertilization of oocytes and incubation of fertilized oocytes or embryos.

The reference by Martino is relied upon as explained above for the disclosure of a method of oocyte cryopreservation by rapid cooling of oocyte suspension in vitrification solution with EG as intracellular cryoprotectant. The reference is silent about equilibration of the oocyte suspension with the intracellular cryoprotectant. However, the reference by Papis et al. teaches that a gentle pre-equilibration of oocyte for about 12-15 minutes at near physiological temperature of about 32-35 degree C in the solution with EG enables saturation of oocytes with the cryoprotective agent such as EG and that equilibration/saturation of oocytes with the intracellular or permeating cryoprotective agent is a prerequisite of successful vitrification. The reference by Papis et al. also recognizes beneficial effects of rapid cooling rate on cryopreserved oocytes. It teaches a direct dropping of oocyte-containing microdroplets into liquid nitrogen wherein the microdroplets have volume of 6 microliters.

The references by Martino et al. and by Papis et al. teach the use of a base medium TCM 199 comprising serum for preparing the suspensions of oocytes. The reference by Martino et al. indicates the use of matured oocytes. The reference by Papis et al. clearly teaches cryopreservation of matured and denuded oocytes or the use of oocytes that have cumulus cells removed prior exposure to the equilibration solution in the method for oocyte cryopreservation.

Both cited references by Martino et al. and by Papis et al. disclose the use of mammalian oocytes, storing oocytes for at least several hours, thawing the frozen oocytes, fertilizing and incubating the fertilized oocytes or embryos. The reference by Martino et al. discloses a protocol of thawing such as thawing time of about 3 minutes at temperature of about 39 degree C that is similar to the claimed thawing procedure.

Both cited references teach successful cryopreservation by rapid cooling of microdroplets with oocyte suspensions and further fertilization of thawed oocytes.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use a gentle equilibration of oocytes with the intracellular permeating cryoprotectant such as EG in the cryopreseravtion method of Martino with a reasonable expectation of success in cryopreservation of oocytes as clearly taught by Papis et al. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 46-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martino et al. {IDS reference; Biology of Reproduction. 1996. 54:1059-1069) and Papis et al. {IDS reference; Theriogenology. 1999, page 173.) as applied to claims 46-51, 54-62 and 64-66 above, and further in view of Arav et al. {Journal of Reproduction and Fertility. 1993, 99: 353-358}, Saha et al. {IDS reference; Cryobiology. 1996. 33:291-299} and Liu et al. {IDS reference; Biology and Reproduction.1995. 53:786-790}.

Claims 46-51, 54-62 and 64-66 as explained above. Some claims are further drawn to the use of trehalose as a sugar in the vitrification solution and to the use of polyvinylpyrrolidine (PVP) as a macromolecule in the solution(s). Some claims are further drawn to culturing fertilized oocytes in KSOM medium in co-culture with cumulus cells.

Both cited references by Martino et al. and by Papis et al. teach successful cryopreservation of oocytes by rapid cooling of microdroplets with oocyte suspensions and further fertilization of thawed oocytes wherein the cryoprotective solutions comprises intracellular permeating cryoprotectant EG and sugar. In particular, the cryopreservation methods disclosed by Martino et al. and by Papis teach the use of sucrose as a sugar in the vitrification solutions.

Thus, the references by Martino et al. and by Papis et al. are missing disclosure about the use of trehalose as cryoprotectant. However, the reference by Arav et al. teaches that trehalose is a suitable oocyte cryoprotectant and that exposure of oocytes to trehalose is less harmful than exposure to sucrose (abstract).

The cited references by Martino et al. and by Papis et al are silent about the use of a macromolecule such as polyvinylpyrrolidine (PVP) in the cryopreservation solutions with EG

and sugar. However, the reference by Saha et al. teaches the efficiency of EG, trehalose and PVP in the solutions for successful vitrification and cryopreservation of in vitro fertilized oocytes (title or abstract).

Further, the reference by Liu et al. is relied upon to demonstrate that culturing fertilized oocytes in KSOM medium in co-culture with cumulus cells is known in the prior art (page 787, col.1, last par.).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute sugar trehalose for sugar sucrose in the vitrification solutions intended for preservation of oocytes with a reasonable expectation of success in cryopreserving of oocytes in the vitrification solution because prior art teaches and suggests this sugar substitution as particularly beneficial for mammalian oocytes including bovine oocytes. One of skill in the art would have been motivated to use PVP in the cryoprotecting agent containing solutions with EG and sugar trehalose because this combination has been taught and suggested as effective for oocyte vitrification and cryopreservation. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103

Response to Arguments

Applicant's arguments with respect to the canceled claims 36-45 and to the new claims 46-65 have been considered but are moot in view of the new ground(s) of rejection.

Claim rejection(s) over US 5,780,295 and WO 99/66271 have been withdrawn in the instant office action because the new pending claims are totally refocused away from the specific properties of a solid surface in the method for cryopreservation of generic biological material towards the newly introduced limitations drawn to composition(s) of cryoprotective solution(s) in the method for cryopreservation of oocytes.

With regard to the reference by Martino et al. the applicants' argument (response page 5, last par.) that it teaches the sole of plastic straws as a surface for cryopreservation is not found persuasive because this reference also teaches the use of a metal grid as a solid surface providing for ultra-rapid cooling rates in the method for cryopreservation of oocytes. Moreover, the plastic straw surface is "a solid surface" within the meaning of the instant claims.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Vera Afremova

AU 1651

April 21, 2004

IRENE MARX
PRIMARY EXAMINER